Correction of Acidosis in Hemodialysis Patients Increases the Sensitivity of the Parathyroid Glands to Calcium

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Abstract. Correction of acidosis in hemodialysis patients increases the sensitivity of the parathyroid glands to calcium. In this study, the parathyroid response to the correction of acidosis in eight hemodialysis patients was determined by performing dynamic assessment of parathyroid function before and after the correction of acidosis. The parathyroid response to intravenous calcitriol before and after the correction of acidosis was also assessed. After optimal correction of acidosis, there were no significant changes in blood pH, ionized calcium, phosphate, or alkaline phosphatase values, but the level of venous total CO₂ increased significantly. Parathyroid hormone/ionized calcium curves were displaced downward after correction of acidosis, but not after the administration of intravenous calcitriol. The correction of metabolic acidosis in hemodialysis patients with secondary hyperparathyroidism can suppress parathyroid hormone secretion by increasing the sensitivity of the parathyroid glands to ionized calcium. (J Am Soc Nephrol 8: 627–631, 1997)

Acidosis has widespread effects on metabolism in patients with chronic renal failure. It increases protein degradation and amino acid oxidation (1), and its correction is associated with an improvement in insulin-mediated glucose disposal (2). Acidosis is also associated with osteomalacia and osteopenia (3). Initially this was thought to be the result of low levels of 1,25-dihydroxyvitamin D (1,25(OH)₂D₃) secondary to decreased renal 1-alpha-hydroxylase activity (4,5), but this has been questioned recently (6). Acidosis also has a direct effect on bone through the buffering of protons by carbonate, leading to depletion of bone mineral (7). Thus, directly and indirectly, acidosis predisposes to the development of osteomalacia. That acidosis may have a role in the development of hyperparathyroidism has been suggested by studies showing that acidosis enhances circulating parathyroid hormone (PTH) (8), that optimal correction of acidosis in hemodialysis patients can delay the progression of hyperparathyroidism (9), and that PTH is independently and negatively correlated with GFR, and plasma bicarbonate and 25(OH)D₃ levels (10). To examine the hypothesis that this is secondary to a decrease in the sensitivity of the parathyroid glands to either calcium or 1,25(OH)₂D₃, the PTH/ionized calcium (iCa⁺⁺) relationship has been studied in hemodialysis patients before and after the correction of acidosis.

Materials and Methods

Patients

Eight (five male, three female) hemodialysis patients were studied (Table 1). All patients gave written informed consent, and the study protocol was approved by the Joint Ethics Committee of the University of Newcastle upon Tyne and Newcastle Health Authority. Ages ranged from 26 to 60 (median, 54). All had persistent acidosis, as evidenced by a mean predialysis total CO₂ of less than 22 mmol/L for the 3 months prior to the study. All patients had an immunoreactive PTH (iPTH) level of greater than 120 ng/L, and none had previously received treatment with vitamin D analogues. Subjects with severe hyperparathyroidism (iPTH > 1000 ng/L) and those with diabetes mellitus were excluded from the study. All subjects underwent hemodialysis with cellulosic dialyzers and bicarbonate dialysate (35 mmol/L). The dialysate flow rate was 500 mL/min. The blood flow rate depended on vascular access (five fistulae, three permanent venous catheters). PTH/ionized calcium curves were generated on four occasions for each subject: acidic pre- and postcalcitriol, and after correction of acidosis pre- and postcalcitriol.

Protocol

The study consisted of two 6-wk periods, the order of which was randomly assigned, separated by a 2-wk "wash-out". During one period (acid), patients underwent standard dialysis (dialysate bicarbonate, 35 mmol/L) for 4 wk, at the end of which iPTH/iCa⁺⁺ curves were generated. During the fifth week, patients were given 2 μg calcitriol (Calcijex; Abbott Laboratories, Chicago, IL) intravenously after each dialysis (6 μg total), and iPTH/iCa⁺⁺ curves were generated at the end of the sixth week. During the other period (bicarbonate), the dialysate bicarbonate concentration was increased to 40 mmol/L, iPTH/iCa⁺⁺ curves were generated before and after the administration of intravenous calcitriol, as previously described. During the generation of the iPTH/iCa⁺⁺ curves, subjects were always dialyzed against a concentrate containing 35 mmol/L bicarbonate to exclude an acute effect. The curves were generated by dialyzing subjects against a dialysate containing 0 mmol/L calcium, followed by dialysis against a dialysate with 2.5 mmol/L calcium, the intention being to lower and then raise whole-blood ionized calcium during one dialysis session to 0.9 and 1.5 mmol/L, respectively, thus maximally stimulating and then suppressing PTH release. Throughout the study, blood was taken from the “arterial” limb of the dialysis circuit at regular intervals, iCa⁺⁺ was measured immediately, and plasma was
stored at −70°C before iPTH analysis. For any given concentration of serum calcium, the serum PTH level is always higher during the induction of hypocalcemia than it is during the recovery from hypocalcemia (11). To avoid this hysteresis, paired samples for iPTH and iCa++ were analyzed only when the calcium level was rising from 0.9 to 1.5 mmol/L. Plasma 1,25(OH)2 D3 concentration was measured on a predialysis sample taken before the generation of iPTH/iCa++ curves in the fourth and sixth weeks.

**Assays**

Intact parathyroid hormone (1–84) was measured by an immunoradiometric assay (Allegro, Nichols Institute, San Juan Capistrano, CA). The normal range for this assay is 10 to 65 ng/L. Plasma concentration of 1,25(OH)2 D3 was measured using a double-antibody RIA (Allegro, Nichols Institute, San Juan Capistrano, CA). The normal range for this assay is 18 to 62 ng/L. Ionized calcium was measured on whole blood at actual pH using an ion-specific probe (Ciba Corning 634 Ca++/pH Analyser; Ciba Corning Ltd, Halstead, Essex, UK). Total calcium, phosphate, total CO2, and alkaline phosphatase values were measured by standard laboratory techniques.

**Statistical Analyses**

Values are reported as means ± SE unless otherwise stated and are analyzed using paired t tests. P < 0.05 was considered statistically significant. Immunoreactive PTH results were ln transformed and plotted against the corresponding iCa++ value (12). Using linear regression, the slope and the intercept on the ordinate at an iCa++ value of 1 mmol/L were calculated. The mean values for the slope and the intercept were compared by the Wilcoxon signed rank test.

**Results**

**Subjects With Arteriovenous Fistulae or Permanent Venous Catheters**

Subjects 2, 3, and 8 had permanent venous catheters; the other subjects had arteriovenous fistulae. There was no significant difference between these two groups in the prestudy levels of tCO2, whole-blood pH, iCa++, or phosphate levels (tCO2: cannulae 18.6 ± 0.3 versus fistulae 18.6 ± 0.8 mmol/L; pH: cannulae 7.38 ± 0.04 versus fistulae 7.39 ± 0.08; iCa++: cannulae 1.14 ± 0.07 versus fistulae 1.16 ± 0.03 mmol/L; phosphate: cannulae 2.08 ± 1.01 versus fistulae 2.10 ± 0.95 mmol/L). Total CO2, pH, Ionized Calcium, Phosphate, and 1,25(OH)2 D3 Values

The plasma tCO2 level was significantly higher after 4 wk of treatment with a dialysate bicarbonate of 40 mmol/L (bicarbonate 25.3 ± 1.6 versus acid 18.6 ± 0.8 mmol/L, P < 0.001). Venous whole-blood pH, iCa++, and plasma phosphate levels were not significantly different between the two treatment groups (pH: bicarbonate 7.39 ± 0.03 versus acid 7.38 ± 0.04; iCa++: bicarbonate 1.31 ± 0.6 versus acid 1.31 ± 0.04 mmol/L; phosphate: bicarbonate 2.23 ± 0.08 versus acid 2.12 ± 0.02 mmol/L). Plasma 1,25(OH)2 D3 concentrations were not significantly different in the acid and bicarbonate periods, and there was no significant change in the concentration after calcitriol treatment (acid pre-calcitriol 12.1 ± 2.0, acid post-calcitriol 17.1 ± 2.8; bicarbonate pre-calcitriol 11.4 ± 1.6, bicarbonate post-calcitriol 24.4 ± 8.4 ng/L).

**iPTH/iCa++**

After the correction of acidosis, the iPTH/iCa++ curves moved downward and to the left in the majority of subjects, suggesting significant suppression of PTH release (Figure 1). There was no additional suppression in either the acid or the bicarbonate phase of the study after therapy with calcitriol. Because the PTH response to calcium is not linear, and because of the heterogenous nature of the curves, the iPTH/iCa++ curves were linearized by ln transformation. The linear regression equations for most subjects demonstrate a significant change in the intercept on the ln PTH axis at all concentrations of iCa++. For an iCa++ level of 1 mmol/L, the intercepts were: acid pre-calcitriol 5.99 ± 0.12 versus bicarbonate pre-calcitriol 5.40 ± 0.13, P < 0.005. Using the linear regression equations, ln PTH values were calculated for values of iCa++ ranging from 0.8 to 1.5 mmol/L. The results were then amalgamated (Figure 2). After correction of acidosis, the majority of plots have moved downward and toward the left, suggesting a significant suppression of PTH release. There was no significant change in slope after correction of acidosis, before or after therapy with calcitriol (acid pre-calcitriol: 3.75 ± 0.56 versus acid post-calcitriol 3.92 ± 0.53; bicarbonate pre-calcitriol 3.73 ± 0.41 versus bicarbonate post-calcitriol 3.84 ± 0.42).

**Table 1. Patient characteristics at the time of entry into study**

<table>
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<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>tCO2 (mmol/L)</th>
<th>iPTH (ng/L)</th>
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* tCO2, total CO2; iPTH, immunoreactive parathyroid hormone; RV, renovascular disease; CPN, chronic pyelonephritis; GN, glomerulonephritis; Ob Uro, obstructive uropathy.
Figure 1. Ionized calcium (iCa\(^{++}\))/immunoreactive parathyroid hormone (iPTH) plots of subjects before (○) and after (●) correction of acidosis, but before treatment with 1,25(OH)\(_2\) D\(_3\).

**Discussion**

In this study, the hypothesis that acidosis decreases the sensitivity of the parathyroid glands to calcium or calcitriol has been examined by performing dynamic parathyroid assessment of PTH secretion in eight HD patients, before and after the correction of acidosis, and before and after intravenous calcitriol administration. The results demonstrate that after the correction of acidosis, the sensitivity of the parathyroid glands to iCa\(^{++}\), within the physiological range, increases. Intravenous calcitriol had no effect on PTH secretion, either before or after the correction of acidosis. That acidosis affects PTH secretion has previously been demonstrated. In animal experiments and
cross-sectional studies of uremic patients, there is a correlation between plasma bicarbonate and intact PTH (8,13). St John et al. (10) found that iPTH is negatively and independently correlated with GFR, plasma bicarbonate, and 25(OH)D3 levels. However, this is the first study to demonstrate that correction of acidosis decreases PTH secretion, when a sensitive assessment of parathyroid function is used.

The mechanism for this decrease is uncertain. It is known that many cell functions are pH-dependent, including enzyme activity, ion channel conductance, $O_2$ affinity for hemoglobin, cell growth, and DNA replication (14). This is because buffering of $H^+$ by amino acid residues, particularly the imidazole group of histidine, changes the tertiary structure of proteins and thus their function. The recently cloned $Ca^{++}$ receptor (15) has four acidic amino acid residues characteristic of low-affinity $Ca^{++}$ binding proteins, such as calsequestrin, and these residues are the likely to be the binding sites for extracellular $Ca^{++}$. It is possible that acidosis induces conformational changes in these putative binding residues and reduces their $Ca^{++}$ binding capacity, thus decreasing sensitivity to $iCa^{++}$. In contrast to other studies (16,17), intravenous calcitriol had no effect on PTH secretion. In retrospect this may be related to the dose of calcitriol and the period of time over which it was given (6 $\mu$g in 1 wk). Other authors have given higher doses over longer periods of time; Kwan et al. (12) gave 0.1 $\mu$g per kg body weight oral calcitriol once weekly for 4 wk. Liou et al. (18) compared oral to intravenous calcitriol, but were unable to show any significant inhibition of PTH release until after 6 wk of treatment. Because of these results, the possibility that acidosis decreases the sensitivity of the parathyroid glands to calcitriol has not been excluded. This needs to be examined with studies including a longer period of treatment with calcitriol.

It is clear from this and other studies that optimal correction of acidosis is an essential component of adequacy of dialysis. How can this be achieved in hemodialysis? At the start of renal replacement therapy, there is a large buffer deficit, accumulated during the predialysis period of prolonged positive hydrogen balance, and this buffer needs to be replaced (19-21). During this initial period, predialysis bicarbonate concentration remains low despite optimal postdialysis bicarbonate concentrations. When buffer stores are replenished, the predialysis bicarbonate concentration depends on the hydrogen ion generation rate, a function of protein intake (19). Therefore the dialysate bicarbonate concentration must be individualized and, if necessary, oral sodium bicarbonate administered to achieve a predialysis $tCO_2$ value $>$22 mmol/L and a postdialysis $tCO_2$ value between 28 and 32 mmol/L to avoid postdialysis alkalosis (22).

In conclusion, we have shown that correction of acidosis increases the sensitivity of the parathyroid glands to $iCa^{++}$, and that optimal correction of acidosis in hemodialysis is an essential component of adequate dialysis.

Acknowledgments

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References

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